Chest electrical impedance tomography examination, data analysis, terminology, clinical use and recommendations: consensus statement of the TRanslational EIT developmeNt stuDy group

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ONLINE SUPPLEMENT 8

Clinical use of EIT in neonatal and pediatric patients

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Introduction

EIT offers unique potential as a clinical tool in the pediatric and neonatal population, both to monitor physiological states and to direct therapy and interventions. Currently there is need for improved technologies to guide respiratory care in children. In general, bedside cardiorespiratory monitoring is more difficult in pediatric patients (1). In addition, traditional modes of cardiorespiratory imaging require patient cooperation, expose the patient to radiation or are unacceptably invasive for children. Uncuffed endotracheal tubes (ETT) and the trend towards exclusive or early non-invasive ventilation (NIV) modes, further complicates respiratory monitoring in infants and children (2, 3). EIT, by virtue of being non-invasive, radiation-free, portable, independent of an ETT and allowing multiple physiological information to be extracted from a single recording, fulfils the criteria of an ideal pediatric lung monitor for the modern era.

The role of respiratory monitoring in improving outcomes in pediatric and neonatal lung disease is well established (4-7). Increasing awareness of the differences in the regional behaviour of the diseased pediatric lung, particularly in diseases characterized by atelectasis (such as infant respiratory distress syndrome (RDS)), and a lack of existing lung monitoring tools, has been the attention of previous pediatric studies of EIT in the clinical setting as well as animal models. To date, most studies have focused on monitoring (regional) changes in lung aeration and ventilation and, to a lesser extent, lung perfusion, with the aim of improving basic knowledge on lung physiology and better understanding the interaction between the impact of lung disease and clinical interventions on lung function. As of July 2015, we identified 48 articles reporting on EIT examinations of preterm and term neonates, infants and children with the total of 1018 subjects studied. Our search was primarily based on the PubMed database (National Center for Biotechnology Information, U.S. National Library of Medicine 8600 Rockville Pike, Bethesda MD, 20894 USA).

This electronic online supplement (EOS) reviews the existing literature involving EIT in the pediatric and neonatal populations, hindrances to clinical use and suggests areas for further development.

Understanding the physiological principles of the respiratory system in the healthy and diseased state

Regional patterns of tidal ventilation, end-expiratory lung volumes (EELV) and mechanics in the newborn, infant and pediatric lungs are poorly understood. Safe and effective respiratory care involves understanding the physiological state of the respiratory system. This is particularly relevant in the diseased lung, where physiological states cannot be assumed to be uniform throughout all lung units. The regional and global physiology of the respiratory system during pediatric disease states has been well described in animal models (8-12) but the lack of practical bedside tools to measure regional physiology has hampered confirmation of these principles in human subjects. EIT has been extensively used to fill this research gap, and the literature can be generally considered to demonstrate the ability of EIT to describe gravity-dependent and right-to-left differences in volume states and mechanics. A few preliminary studies investigating ventilation-perfusion relationships with EIT offer a new promising research pathway and may lead to better understanding of the complex interaction of ventilation and lung perfusion (13-16).

- **Gravity-dependent inhomogeneity**

a. End-expiratory lung volume

The susceptibility of the acutely diseased adult lung to the gravity-dependent inhomogeneity of EELV is well known (17). Radiological methods to describe gravity-dependency and volume states are not practical in pediatric patients. The group of van Kaam and co-workers used EIT to describe end-expiratory patterns in RDS of prematurity (18). This group further described the interaction between applied pressure and regional volumes in 15 infants subjected to a stepwise oxygenation-guided recruitment procedure during high-frequency oscillatory ventilation (HFOV). During each incremental and decremental step in mean airway pressure the changes in EELV were recorded and used to reconstruct the inflation and deflation limbs of the individual pressure-volume relationship of the lung. The study confirmed that regional lung hysteresis is present in preterm infants with RDS (18). It also showed that the regional (dependent versus non-dependent) changes in EELV were highly variable and did not always follow the well-defined gravity-dependent pattern seen in adult RDS. The hysteresis pattern identified was similar to those described in the whole lung using respiratory inductive plethysmography (19). This similarity was directly confirmed later when it was shown that EELV changes measured by

EIT in a cross-sectional slice of the lung are representative of the changes in the whole lung measured by respiratory inductance plethysmography (20). In a separate analysis of the EELV changes over time, this group described, for the first time, the gravity-dependent pattern of the time constant of the lung in preterm infants with RDS; both before and after exogenous surfactant therapy (21).

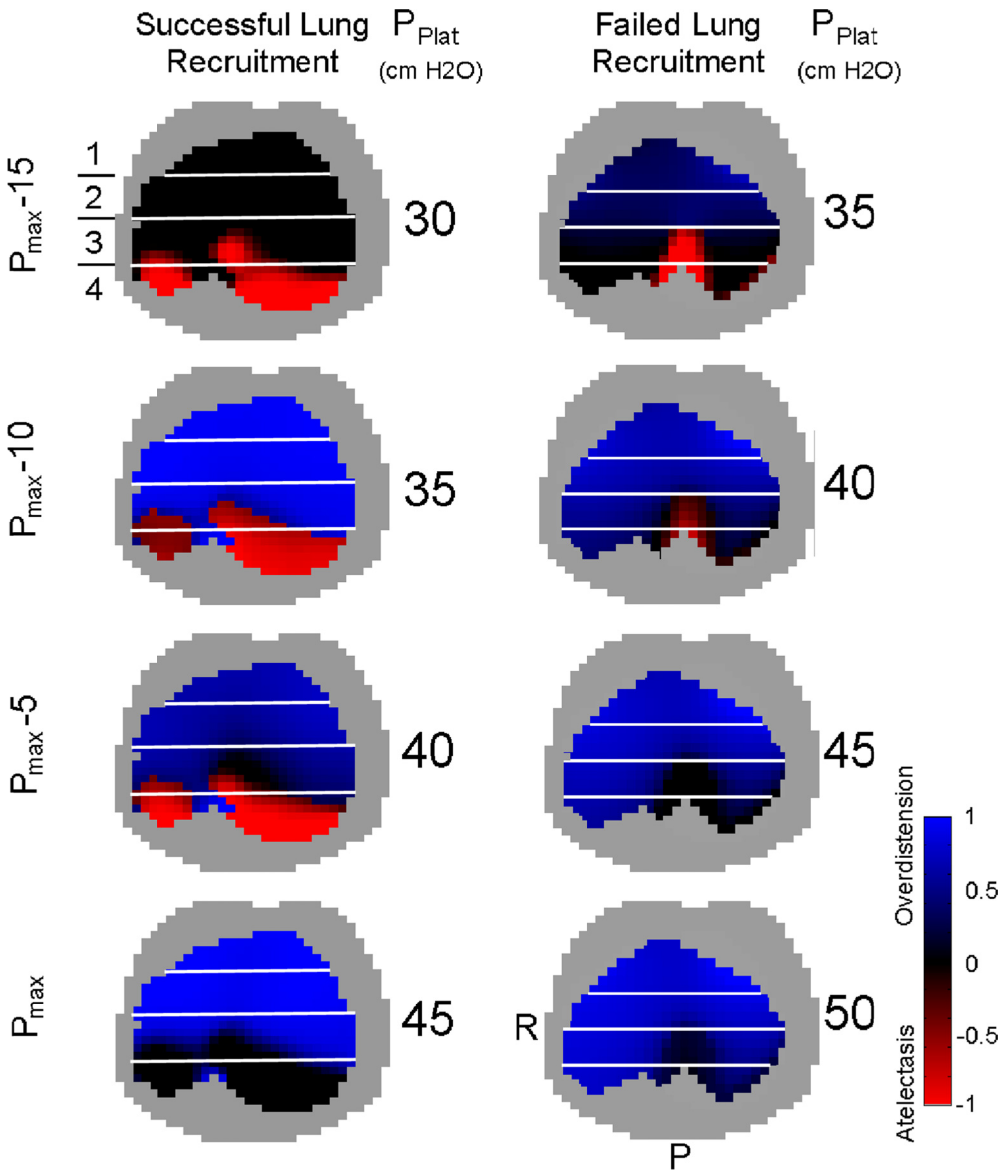

Figure E8.1. EIT images of a pediatric lung recruitment maneuver, atelectasis in red and overdistension in blue. Left column shows a responder to lung recruitment, right column shows a nonresponder. The corresponding plateau pressure is shown to the right of each EIT scan. The lung area is divided into four regions of interest. "Pmax" on the left of the image means clinical recruitment (reached sum of arterial partial pressures of O_2 and CO_2 of > 400 mm Hg) in responders or reaching the maximal plateau pressure of 50 cm H_2O without improvement in gas exchange in nonresponders. (Data originate from the study (22).)

EIT has been used to define regional EELV states during a stepwise PEEP recruitment maneuver in pediatric RDS (22, 23). In these studies EIT was able to classify lung areas as atelectatic, overdistended or normally ventilated. Atelectasis was found to be predominant in the posterior (dependent) lung areas. It was shown on EIT images that all posterior atelectatic lung areas need to be completely recruited in order to achieve physiologic lung opening, as defined by a significantly improved gas exchange. The pressures used to recruit posterior lung areas always produced significant overdistension of anterior (nondependent) lung areas. Most of the patients responded to a stepwise increase in plateau pressures (defined as "responders"), and those responders had large amounts of posterior atelectasis prior to lung recruitment. A few patients in these studies did not respond to high plateau pressures, as evidenced by no improvement in gas exchange, and those patients had almost no atelectasis on EIT. Overall, large amounts of atelectasis on EIT images significantly increased the chance of responding to lung recruitment (Figure E8.1) (22).

In summary EIT has the potential to be a powerful monitoring tool for detecting changes in EELV either as a result of an intervention or as a result of progression/improvement of lung disease.

b. Tidal volume

EIT has been used to deepen our understanding of the distribution of tidal ventilation in infants. Longstanding principles suggested a reversal of the adult pattern of tidal ventilation distribution in infancy (24). EIT studies in spontaneously breathing healthy infants have repeatedly shown this to be an oversimplification. The distribution of tidal ventilation is highly variable, almost on a breath-to-breath basis and influenced by magnitude of tidal effort, respiratory rate and pattern, EELV, body position and even neck position (25-27). Gravity was found to be a significant factor in the ventilation distribution in 32 spontaneously breathing healthy infants examined by EIT in the neonatal period, and at 3 and 6 months of life (28). Riedel and co-workers demonstrated similar findings in a population of 17 healthy term infants, also identifying that gravity had a greater effect on regional tidal ventilation patterns in spontaneously breathing preterm infants, with greater relative tidal ventilation in the non-dependent lung (29). This study compared EIT with the multiple breath washout technique for measuring regional ventilation, finding higher repeatability and better discrimination of regional patterns using EIT. Interestingly, a study by van den Burg and co-workers (30) in preterm infants on nasal continuous positive airway pressure (CPAP) showed that changing from supine to prone positioning increased tidal ventilation in the ventral, dependent lung regions. Lupton-

Smith and co-workers identified highly variable gravity-dependent patterns of ventilation in 55 infants and children between 6 months and 9 years (27). Lying on the left side resulted in significantly better ventilation of the left, but lying on the right produced equal ventilation patterns.

In the diseased infant lung, the feasibility of EIT to monitor tidal ventilation has been long established (31). EIT has been used to demonstrate significant regional breath-to-breath variability in the distribution of delivered tidal volume (V_T) during synchronized mechanical ventilation even using tightly controlled, and constant, V_T delivery (volume-guarantee) modes in preterm infants (32). This study supports the previous observations made in healthy infants regarding the complex behaviour of the tidal ventilation within the mild to moderately diseased preterm infant lung, and also demonstrated similar gravity dependent changes associated with prematurity. Post-menstrual age was also found to influence the distribution of tidal ventilation during conventional ventilation. The authors postulated that the age-related changes were due to differences in airway calibre associated with the primary reason for respiratory support; infant RDS in early life and evolving or established chronic lung disease of prematurity later (32). In summary, EIT has changed our understanding of regional ventilation distribution in the infant lung and is highly suitable to monitor ventilation inhomogeneities in these populations.

c. Lung mechanics

Understanding lung mechanics is essential to optimal delivery of therapy for pediatric lung diseases. Studies in animal models of pediatric and neonatal RDS, many using EIT, have demonstrated significant regional differences in respiratory system compliance (8, 10, 12, 33-36), time constants and filling characteristics of the lung (37). To date these findings have not been replicated in human studies and the use of EIT to better understand regional lung mechanics has been limited to the observational study of time constants in 22 preterm infants with acute RDS receiving an open lung maneuver during HFOV (21). This study identified distinct differences in the time constant of the lung depending on whether ventilation was on the inflation or deflation limb of the pressure-volume relationship, and the surfactant state of the lung at the time. The authors postulated that these differences were due to changes in respiratory system compliance, a reasonable conclusion although this could not be directly measured, due to the difficulties in bedside quasi-dynamic compliance measurements during HFOV (38). The findings though were similar to those in pediatric and neonatal animal models receiving an open lung maneuver, where direct measures of lung mechanics were possible (8, 12, 39). In summary, the measurement of the volume pressure relationship using EIT needs further exploration, particularly as significant differences in regional visco-elastic properties are likely to be present in acute pediatric and infant lung diseases.

- **Right versus left lung asymmetry**

Right to left lung asymmetry is not generally recognized as a component of pediatric lung disease. EIT is well suited to defining right to left lung asymmetry and has allowed these assumptions to be challenged. In particular, the observations in spontaneously breathing term and preterm infants that right to left lung asymmetry is markedly influenced by relatively minor events such as turning of the head from one side to another or body position are important (25, 26). In mechanically ventilated infants body and head position only influenced ventilation symmetry in the left lung and only during prone (26).

In piglets, accurate identification of ETT position within the respiratory tree and oesophagus is possible with EIT, and superior to current bedside tools (40). This was confirmed in a clinical study on pediatric patients scheduled for routine cardiac catheterization (41). Prior to the intervention requiring anesthesia and endotracheal intubation, the children were examined by EIT during intentional positioning of ETT in the right main bronchus and after its correction. The authors concluded that right to left lung symmetry could be used to confirm ETT position.

- **Breathing patterns**

EIT has been used to demonstrate that breathing patterns, particularly rate and effort, strongly influence the distribution of tidal ventilation in spontaneously breathing healthy infants (25). The observation that deep sighs and shallow small tidal breathing patterns result in different patterns of ventilation distribution has questioned the traditional understanding that infant and adult ventilation distribution differs fundamentally. More importantly, the ability of EIT to make multiple prolonged intra-subject recordings has shown that the ventilation distribution is a highly complex phenomenon in the human lung. Since EIT measurements do not interact with the breathing pattern of the subject, EIT is an ideal instrument to explore not only breathing pattern but also changes in regional ventilation distribution over time, i.e. during REM and NREM sleep.

- **Lung perfusion**

The distribution of lung perfusion in the diseased pediatric lung is poorly understood, especially in newborn infants. The presence, and clinical significance, of mis-matching of regional ventilation and perfusion is greater during active lung disease or right heart disease. EIT may offer potential to monitor both ventilation and perfusion (16, 42, 43). To date, studies in infants and children on EIT-derived lung perfusion have been limited. A single study in 26 preterm infants of varying postnatal age receiving synchronized conventional mechanical ventilation showed that gravity-dependent differences in the EIT signal within the cardiac domain (approximating relative perfusion) were present in the right lung (13). The non-dependent lung regions contributed a greater component of the perfusion than the dependent regions. This study showed that these differences were greatest in the first week of life. These findings contributed to similar gravity-dependent differences in ventilation-perfusion matching, with greater regional mismatching in infants less than a week old and requiring any form of oxygen therapy.

Schibler and co-workers used the same EIT image reconstruction and filtering methodology to evaluate 18 spontaneously breathing infants before and after ventricular septum defect surgery, where a known and well established change in pulmonary circulation results. A decrease in EIT-derived perfusion (with increased ventilation-to-perfusion ratios) was seen in the middle and non-dependent regions of the lung following ventricular septum repair (44). The role of EIT in assessing lung perfusion needs further clarification.

The following Table E8.1 provides an overview of EIT studies enhancing our knowledge of neonatal/pediatric lung physiology.

Physiological principle addressed	Intention of study	Description of study subjects (age, disease, mode of support)	Type of EIT imaging	Physiological measures	Summary of results	References
Lung hysteresis	Confirming existing concepts using human subjects	1. Preterm infants (RDS) receiving HFOV, surfactant and a recruitment maneuver 2. Pediatric RDS patients n=15 (18) n=15 (45) n=9 (23)	Raw time course data	EELV	1. Confirmed regional lung hysteresis in preterm RDS. 2. Surfactant therapy rapidly improved and stabilized regional EELV. 3. Effect on EELV was most prominent in the dependent lung regions. 4. Atelectasis predominated in dependent lung regions and overdistension in non-dependent regions in pediatric RDS. 5. Response to lung recruitment depended on the degree of lung atelectasis.	(18, 23, 45)
Tidal volume	Identified new concepts	Healthy infants and children n=10 (26) n=56 (27) n=32 (28) n=12 (25) n=24 (46)	fEIT images	V_T distribution	1. Tidal ventilation distribution was highly variable and influenced by many factors. 2. Distribution followed gravity dependent patterns in infants. 3. Lying on the left and right did not produce similar ventilation patterns in children.	(25-28, 46)
	Identified new concepts	Preterm and term infants with RDS n=20 (30) n=1 (31) n=27 (32)	fEIT images	V_T distribution	Tidal ventilation was posture-dependent and demonstrated highly variable patterns on a breath-to-breath basis.	(30-32)

Physiological principle addressed	Intention of study	Description of study subjects (age, disease, mode of support)	Type of EIT imaging	Physiological measures	Summary of results	References
Right-to-left lung asymmetry	Identify new concepts	Observational studies in term and preterm spontaneously breathing and mechanically ventilated infants n=12 (25) n=10 (26)	fEIT images of ventilation	V_T distribution	1. Different patterns of right and left lung ventilation were seen in prone, supine and lateral positioning (especially in left lung) during spontaneous breathing. 2. Head position influenced symmetry of ventilation. 3. These patterns were lost in mechanically ventilated infants, except when positioned prone.	(25, 26)
Right-to-left lung asymmetry	Identify new concepts	18 children requiring anesthesia and endo-tracheal intubation prior to heart catheterization	fEIT images of ventilation	V_T distribution	Increase in right lung ventilation was found after intentional intubation of the right main bronchus. The right-to-left asymmetry was reduced after the ETT placement in trachea. Cases of un-intended left main bronchus and oesophagus intubations were identified.	(41)
Lung mechanics	Confirm existing concepts in human studies	22 preterm infants (RDS) receiving HFOV	Raw time course data	Time constant of respiratory system (actual and modelled data)	Differences in the time constant of the lung related to the volume state and position on quasi-static pressure-volume relationship of the lung.	(21)
Breathing patterns	Confirm existing concepts and identify new concepts	Term and preterm spontaneously breathing infants n=12 (25) n=10 (26)	EIT waveforms, fEIT images of ventilation distribution	Breathing rate and regional V_T	1. High variability of spontaneous neonatal breathing rate and V_T was confirmed. 2. Regional ventilation distribution is instantaneously modified by changes in the breathing pattern.	(25, 26)

Physiological principle addressed	Intention of study	Description of study subjects (age, disease, mode of support)	Type of EIT imaging	Physiological measures	Summary of results	References
Lung perfusion	Confirming existing concepts	26 preterm infants (RDS) (13) and 18 spontaneously breathing infants before and after VSD repair (44)	fEIT images filtered to respiratory and cardiac domains	Tidal ventilation and heart beat related impedance changes	1. Cardiac signal greater in non-dependent lung regions. 2. Heterogeneous gravity dependent pattern of ventilation-perfusion mismatching. Improved ventilation-perfusion ratios with age and after VSD repair.	(13, 44)

Table E8.1. EIT to understand the physiological principles of the respiratory system in children and infants

EELV: end-expiratory lung volume; ETT: endotracheal tube; fEIT: functional EIT; HFOV: High-frequency oscillatory ventilation; IPPV: intermittent positive pressure–controlled ventilation; PEEP: positive end-expiratory pressure; RDS: respiratory distress syndrome; V_T: tidal volume; VSD: ventricular septum defect

Understanding the interaction between clinical interventions and regional volumetric behavior of the lung

Current cardiorespiratory function monitors generally consider the respiratory system as a single compartment, assuming a uniformity of behavior and response to interventions. As shown in the previous section this incorrectly generalizes and simplifies reality and may, potentially, lead to inappropriate application of respiratory therapies, particularly applied airway pressure.

- **Ventilator-lung interaction**

a. During conventional positive-pressure ventilation

In small observational studies the ability of EIT to demonstrate changes in ventilation patterns correlating to changes in ventilator settings has been established, potentially offering the ability of EIT to guide respiratory support at the bedside (31, 47). In 28 preterm infants, the pattern of regional ventilation whilst receiving synchronized intermittent positive pressure ventilation (SIPPV) with a targeted V_T modality was described by Armstrong and co-workers (32). Meta-analysis of targeted V_T use in prematurity has suggested that this modality offers a modest but clinically important reduction in chronic lung disease (48). To be optimal, it relies on accurate feedback when the mechanical properties of the lung change. This is determined from gas flow at the airway opening, a measure of global mechanical properties. EIT imaging of more than 3000 inflations demonstrated that the regional variability of targeted V_T within the thorax was significantly greater than that estimated at the airway opening. This variability was noted to occur on a breath-by-breath basis, such that all lung regions frequently experienced rapidly changing tidal ventilation. This observational study was unable to conclude whether alternative PEEP levels would have altered this variability, but this study highlights the limitations, and assumptions, of many common bedside respiratory function monitors that consider the respiratory system as a single compartment, and the potential of EIT to be integrated into modern feedback driven respiratory support modalities.

b. During non-invasive respiratory support

The main goal of non-invasive respiratory support is the preservation of adequate lung volume during spontaneous breathing without the negative influences of ETT. This limits the ability of accepted bedside tools of respiratory function monitoring. Hough and co-workers measured the effect of body position on regional ventilation distribution in preterm infants receiving CPAP and demonstrated that gravity had little impact (49). The same group also showed that the use of high flow nasal cannula oxygen therapy using flow rates up to 8L/min increases EELV (50). Miedema and co-workers measured changes in EELV and ventilation distribution during different levels of nasal CPAP in 22 stable preterm infants (51). They showed that increasing CPAP from 2 to 6 cmH_2O resulted in a homogenous increase in EELV. This optimization of EELV also resulted in more homogeneous distribution of tidal ventilation.

Several studies have also addressed the effect of transitioning preterm infants from either conventional or high-frequency ventilation to nasal CPAP. Carlisle and co-workers have described the regional patterns of EELV and tidal ventilation during and up to 20 min after extubation from positive-pressure ventilation via ETT to CPAP of 6-8 cm H_2O in 10 preterm infants (52). Significant loss of EELV occurred immediately following extubation, and recovery was variable and not predicted from the post-extubation oxygen requirements. EELV losses in the dependent lung regions were more persistent than in the non-dependent, and resulted in increased ventilation inhomogeneity. Van der Burg and co-workers measured the changes in EELV in 20 preterm infants extubated from high-frequency ventilation without oscillations (endotracheal CPAP) to nasal CPAP. They report that this transition did not have a clinically relevant impact on EELV (30). V_T increased after extubation but its regional distribution did not change. EIT has also been used to assess changes in EELV and V_T during biphasic positive airway pressure (BiPAP) in stable preterm infants (51). BiPAP using a pressure amplitude of 3 cmH_2O above a continuous distending pressure of 6 cmH_2O, with an inspiration time of 0.5 s, did not have a significant effect on EELV or regional V_T. So far, studies investigating the impact of other modes of non-invasive ventilation on (regional) lung volumes using EIT have been limited.

In summary, non-invasive respiratory modes of support, such as nasal CPAP, high flow nasal cannula, and non-invasive ventilation have become the dominant form of respiratory support in both pediatric and neonatal respiratory critical care (53). The increased popularity of non-invasive support in these populations has often arisen without substantive mechanistic knowledge of the physiological interaction with the diseased lung. EIT offers great potential to address these significant and important shortcomings in knowledge.

c. During high-frequency oscillatory ventilation

EIT has been used in several studies on HFOV in preterm infants with RDS. Initial studies focused on EELV changes during oxygenation-guided open lung HFOV. In addition to clarifying some important physiological principles of the preterm lung as described in the previous section, these studies also showed that EIT has the potential to guide the process of lung recruitment at the bedside by mapping the inflation and deflation limb of the pressure-volume relationship of the lung (18). Reassuringly, the pressure-volume relationships of the lung described by EIT were similar to those described using respiratory inductive plethysmography in term infants (19) and piglets (54) receiving HFOV, and could be described using accepted mathematical models (55). Additional analyses also showed that the basic assumption of a decoupling of oxygenation and ventilation during HFOV was too simplistic (56). Ventilation is not only impacted by the pressure amplitude set during HFV, but also by the changing position of oscillation on the pressure-volume relationship of the lung. As a result the compliance of the respiratory system will change during lung recruitment and thus the subsequent oscillatory volume. This finding, that the volume state of the lung influences lung compliance (and thus V_T), has been supported by more detailed analysis in term infants (57) and preterm lambs (39). Zannin and co-workers also observed, in preterm lambs receiving open lung HFOV, that the regional behavior of EELV, as described by EIT was highly predictive of the point of optimum ventilation and lung mechanics.

- **Surfactant therapy**

EIT is able to detect regional ventilation and aeration changes occurring in the lungs after exogenous surfactant administration. An early case report of a preterm neonate with RDS examined by EIT before and after endotracheal surfactant instillation revealed improved ventilation and right-to-left ventilation symmetry after surfactant (47). Later experimental data acquired in the preterm lamb and surfactant-depletion lavage piglet models of infant RDS showed the ability of EIT to detect not only the ventilation redistribution but also dynamic changes in regional lung filling and emptying and respiratory system mechanics in response to surfactant administration (8, 9, 11, 33, 58, 59). Uniformity of regional ventilation related to effective surfactant therapy was shown to correlate with regional decreases in early molecular markers of injury (11). More recently, Milesi and co-workers demonstrated similar patterns of regional ventilation with EIT in preterm lambs receiving bolus surfactant and surfactant via a novel atomisation system design to be used during non-invasive ventilation (60).

Recently, clinical studies examining the effects of exogenous surfactant administration by EIT have been published. In a study on preterm infants with RDS treated with surfactant, a rapid increase in EELV that was most prominent in the dependent lung regions was detected immediately after recruitment with open lung HFOV. Surfactant also stabilized EELV at much lower mean airway pressures (45). Using raw EIT recordings, it was possible to show that surfactant increased the quasi-static time constant of the respiratory system. In another study, preterm infants with RDS ventilated in the synchronized intermittent positive-pressure and synchronized intermittent mandatory ventilation modes were examined by EIT before, 15 min and 30 min after surfactant therapy (61). Increased aeration and ventilation with improved right-to-left lung symmetry were documented.

- **Role of EIT in body positioning**

It has been known for some time that body positioning of the (preterm) newborn infant can affect lung function. Studies using respiratory inductive plethysmography have shown that left lateral and prone positioning improve EELV, V_T and breathing synchrony (62). Studies using EIT have provided more insight on the distribution of lung volume changes. As discussed in the second section of this EOS, addressing the role of EIT in improving our understanding of neonatal/pediatric lung physiology in response to postural effects, the effect of body positioning on V_T distribution is very variable (25-28, 46).

The effect on EELV has been recently studied by van der Burg and co-workers in preterm infants on nasal CPAP (30). They showed that switching these infants from supine to prone positioning improved EELV and that this increase was most prominent in the dorsal, non-dependent lung regions.

- **Suction of the ETT**

ETT suction is a frequently performed intervention in critical care. By the nature of its purpose, it exposes the lung to intentional derecruitment, with potential consequences on lung volume (63) and cardiorespiratory status (64). A small series of EIT studies have shown that ETT suction, irrespective of how performed, can cause marked, albeit transient loss of EELV in spontaneously breathing infants (65, 66). Whilst global lung volume derecruitment during suction had been well described previously (63, 64, 67), these EIT studies demonstrated regional complexities of volume changes during and after ETT suctions that had previously only been shown in animals receiving muscle-relaxants (68, 69) . The patterns of volume change after ETT suction were highly variable and not always correlated to oxygen needs post-ETT suction. Often EELV losses were quickly regained (65). This has potential clinical importance with regard to how clinicians identify patients needing recruitment maneuvers after ETT suction. Whether the patterns of ventilation change within the lung after suction seen in animal studies occurs in humans requires investigation. Further research in this area is needed but is limited by the lack of realtime pediatric EIT systems.

- **During anesthesia**

Surprisingly, the behavior of the lung during pediatric and neonatal anesthesia has seen little investigations. Humpreys and co-workers identified a significant drop in EELV during induction of anesthesia and intubation in 38 infants and children undergoing elective cardiac surgery, which normalized with commencement of PEEP (70). In contrast, the distribution of ventilation changed from a preferentially dependent lung pattern to non-dependent after induction and starting positive pressure support. This highlights the potential of EIT as a monitoring tool to optimize EELV during clinical interventions.

The following **Table E8.2** summarizes the studies using EIT to examine the effects of clinical interventions on regional lung function.

Clinical problem	Clinical intervention	Patient population	Type of lung disease	Mode of respiratory support	Type of EIT imaging	Physiological measure (EELV, V_T, etc.)	Summary of results	References
Distribution of tidal ventilation during conventional ventilation	SIPPV with VTV	28 stable preterm infants	Preterm RDS and evolving CLD	SIPPV+VTV	fEIT images of V_T	Pattern and variability of V_T	1. V_T distribution was highly variable and changed significantly on a breath-to-breath basis. 2. Current bedside monitoring of V_T under-estimates the variability of V_T within the lung.	(32)
	IPPV and body positioning (supine, prone, quarter-prone)	24 preterm infants 6 sponta-neously breathing infants	RDS	IPPV	fEIT images of V_T	V_T in four image ROIs (anterior, posterior, right left); GI index	1. Ventilated infants had higher global ventilation inhomogeneity than the healthy ones. 2. Ventilation distri-bution among ROIs was not affected by posture in ventilated infants posture-dependent in spontaneous breathing.	(71)
Distribution of tidal ventilation during HFV	Oxygenation-guided open lung HFV	Preterm infants n=15 (18) n=10 (56)	RDS	HFV	Raw images	EELV and V_T	1. Regional hysteresis was present during the open lung maneuver. 2. The P-V relationship of the lung could be mapped and optimal EELV identified. 3. V_T was influenced by the volume state of the lung.	(18, 56)

Clinical problem	Clinical intervention	Patient population	Type of lung disease	Mode of respiratory support	Type of EIT imaging	Physiological measure (EELV, V_T, etc.)	Summary of results	References
Distribution of EELV and tidal ventilation during non-invasive respiratory support	CPAP	22 preterm infants	Prematurity	Nasal CPAP	Raw images	EELV and V_T	1. Increase in CPAP results in homogeneous increase in EELV 2. Increase in CPAP results in more homogeneous distribution of tidal ventilation	(51)
Distribution of tidal ventilation during HFNC	HFNC	13 infants age<1 year	bronchiolitis	HFNC at 8 l/min and 2 l/min	Raw images, fEIT images of V_T	EELV and V_T distribution	HFNC at 8 l/min increased anterior (and global) EELV	(50)
Distribution of EELV and tidal ventilation at extubation	Extubation from SIPPV+VTV Extubation from HFV	Ten stable preterm infants (52) 20 preterm infants (30)	Resolving preterm RDS	SIPPV+VTV and CPAP HFV	Raw data and fEIT images of V_T	EELV and V_T	1. Extubation resulted in significant EELV loss. 2. EELV recovery was variable globally and regionally. 3. EELV is maintained after transitioning from endotracheal to nasal CPAP 4. V_T increases after extubation but its distribution does not	(30, 52)
Exogenous surfactant therapy	Exogenous surfactant administration	15 preterm infants	Acute RDS	Post-recruitment with open lung HFV	Raw data	EELV	Surfactant quickly stabilized EELV, resulted in an optimal EELV at a lower mean pressure and increased time constants	(45)

Clinical problem	Clinical intervention	Patient population	Type of lung disease	Mode of respiratory support	Type of EIT imaging	Physiological measure (EELV, V_T, etc.)	Summary of results	References
Effect of BiPAP on tidal volumes	Cross-over study switching from nCPAP to BiPAP and back to nCPAP	22 stable preterm infants on non-invasive respiratory support	prematurity	BiPAP	Raw data and fEIT ventilation images	EELV and V_T	BiPAP does not impact EELV or V_T	(51)
Effect of body positioning on EELV	Switching from supine to prone position	20 preterm infants	Resolving RDS	nCPAP	Raw data	EELV	Prone positioning increases EELV and favors the ventilation of anterior lung regions	(30)
ETT suction	Closed ETT suction	Preterm infants n=22 (65) n=11 (66)	RDS	HFOV and conventional ventilation	Raw data	EELV	1. Rapid loss of EELV in all regions during ETT suction. 2. Generally rapid resolution of EELV post suction	(65, 66)
Anaesthesia	Induction, intubation and starting positive pressure ventilation	38 infants and children undergoing elective pediatric cardiac surgery	None	Spontaneous-ly breathing to positive pressure support	Raw data and fEIT images of ventilation	EELV and V_T distribution	1. Induction of anesthe-sia and intubation resulted in transient loss of EELV that was rectified using PEEP. 2. Induction of anesthe-sia and positive pressure ventilation resulted in significant changes in ventilation distribution	(70)

Table E8.2. EIT to understand the interaction between clinical interventions and regional volumetric behaviour of the pediatric and newborn human lung.

BiPAP: biphasic positive airway pressure; CLD: chronic lung disease; CPAP: continuous positive airway pressure; EELV: end-expiratory lung volume; fEIT: functional EIT; GI: global inhomogeneity; HFNC: high-flow nasal cannula; HFV: high-frequency ventilation; IPPV: intermittent positive pressure–controlled ventilation; nCPAP: nasal continuous positive airway pressure; PEEP: positive end-expiratory pressure; P-V: pressure volume; RDS: respiratory distress syndrome; ROI: region of interest; SIPPV: synchronized intermittent positive-pressure ventilation; V_T: tidal volume; VTV: volume-targeted ventilation

Use of EIT to guide clinical care in infants and children

For EIT to have any meaningful role in pediatric and neonatal critical and respiratory care, it is essential that EIT be used to guide clinical care with proven evidence of benefit to outcomes. Research aimed at demonstrating a positive clinical outcome using EIT as either a tool to direct therapy (11, 12, 36) or identify the need to alter therapy (40, 72) have been limited to animal model studies. The potential versatility of EIT with regards to clinical environments, therapies, populations and applications would suggest promise as a practical clinical tool. To date, research in this field has been limited to observational studies aimed at demonstrating the feasibility of EIT in a particular clinical role. Generally the proposed clinical pediatric roles for EIT can be classified as either directing applied pressure during artificial respiratory support, monitoring the clinical state of the lung during other therapies or identifying adverse events prior to clinical deterioration.

- **Set applied pressure values**

Lung-protective ventilation settings may vary significantly in the context of the individual lung disease. As RDS is a heterogeneous disease, parameters minimizing alveolar overdistension and atelectasis might be different in each patient, thus warranting a personalized approach (73). No human studies exist yet that have used EIT to prospectively guide the clinical identification and setting of applied pressure values. The ability of EIT to map the relationship between applied pressure and volume state of the lung (18), and track time to volume stability after a pressure change (21), suggests that EIT-guided ventilator algorithms would be possible.

The pressing question as to whether EIT can be effectively utilized to prospectively guide lung protective parameters was first described in an animal model of acute lung injury (12), comparing an EIT-guided algorithm of PEEP-titration to conventional ARDSnet lung protective ventilation in piglets with an induced model of ARDS. Piglets were randomized to receive either EIT-guided ventilation using the open lung concept (74) or ventilation according to the ARDSnet protocol. During EIT-guided ventilation, the level of PEEP was adjusted every two-minutes using real time EIT imaging until all atelectatic areas where recruited. Once atelectasis had resolved in all lung regions, often at the expense of overdistension in previously well-recruited non-dependent areas, PEEP was reduced until overdistension was not evident on EIT but recruitment had been maintained. EIT was then used to guide further intervention if atelectasis re-occurred. Resultant final PEEP levels were higher in the EIT-guided group. Plateau pressures did not differ, reflecting the better compliance and regional volume states (on CT imaging and

EIT) in the EIT-guided group. The EIT-guided group also had less histopathological evidence of lung injury, with improved alveolar capillary vascular permeability. There was excellent correlation between CT and EIT images with regard to volume state of the lung.

More recently, EIT has been used to guide the delivery of a sustained inflation during resuscitation of a newly-born preterm lamb (75). This study found that the time needed to optimally aerate the lung at birth was highly variable, and the EIT-guided sustained inflation group had better gas exchange, lung mechanics, regional ventilation patterns and EELV 60-min after birth than a group of lambs receiving a sustained inflation consistent with current resuscitation guidelines. The same group then extended these findings to compare a sustained inflation (SI) guided by the realtime volume response of the global EIT signal against a pre-determined 30-s SI at birth and an intentional long SI (36). The EIT-guided SI provided the best clinical response and less injury than the 30-s SI. Interestingly, there was no difference in outcomes between the EIT-guided and long SI (still EIT-guided). Importantly, this study demonstrated that EIT might have an interventional role in the Delivery Room, where existing monitoring is limited.

Optimum PEEP was identified in very low birth weight preterm infants ventilated in an assisted mode using EIT during a decremental PEEP trial prior to extubation (76). A simple EIT measure, the ratio between the ventilation of the upper and lower chest region, was used as the decision criterion. The PEEP at which the ventilation distribution was most homogeneous was detected and compared with the empirically set pressure chosen by the attending staff. The EIT-derived PEEP value was significantly higher than the routinely set pressure after extubation to CPAP. The unique feature of EIT used during assisted ventilation is that it allows separate analysis of ventilation distribution during spontaneous and ventilator-generated breaths (31, 77).

These studies show that real time EIT image-guidance could produce a real difference in outcome if properly implemented. Studies involving patients need to follow in order to confirm those promising results.

- **Monitor clinical state of the lung**

Although EIT has been used extensively in small observational trials to describe the clinical state of the lung (see previous section), there have not been any human studies examining the potential to influence outcomes in human infants and children. Such studies will be needed if EIT is to be seen as a valuable alternative to existing bedside monitoring systems.

- **Identify adverse events**

Adverse events are common in pediatric and neonatal critical care (72). The bedside recognition of an adverse event usually requires some form of clinical deterioration, often after a prodromal period in which current bedside monitors fail to detect meaningful change. In this environment, the direct ability of EIT to continually (and without radiation) display the regional V_T states of the lung offers promise as an effective clinical tool. The potential role of EIT to guide ETT suction has been discussed in the previous section. EIT has been shown, in piglets with a controlled pneumothorax, to be able to identify as little as 10 mL of free air in the pleural space, and significantly earlier than any deterioration in oxygen saturation or heart rate (≥100 mL free air) (72). In another study involving piglets, EIT was compared with standard bedside tools (colorimetric capnography, oxygen saturation, heart rate and blood pressure and airway flow) during endotracheal intubation. Whilst all techniques were able to quickly identify oesophageal intubation, only EIT could indicate the location of the ETT within the respiratory tree, specifically whether the ETT was located in the trachea or malpositioned in a main bronchus (40). This was confirmed in a clinical study on children requiring general anesthesia and endotracheal intubation (41). These children were examined by EIT during one-lung ventilation resulting from intentional brief position of ETT in the right main bronchus. The authors demonstrated that the non-intended placement of the tube in the left main bronchus and oesophagus in two children was also correctly identified by EIT. These findings imply that EIT imaging of right-to-left lung ventilation symmetry could be used to determine ETT location without the need for chest radiography.

Data acquired in infants in a routine setting are currently limited to several case reports. Miedema and co-workers presented a preterm infant with a unilateral pneumothorax detected by EIT and confirmed by chest radiography (78). Van der Burg and colleagues published the EIT recording of a preterm infant with unilateral atelectasis (79). Figure E8.2 shows a case of a ventilated neonate in whom a highly asymmetric ventilation distribution identified by EIT led to the detection of an ETT malposition. The ventilation distribution improved immediately after the intubation depth had been reduced by ETT withdrawal and was confirmed during a repeated EIT examination carried out 6 min later.

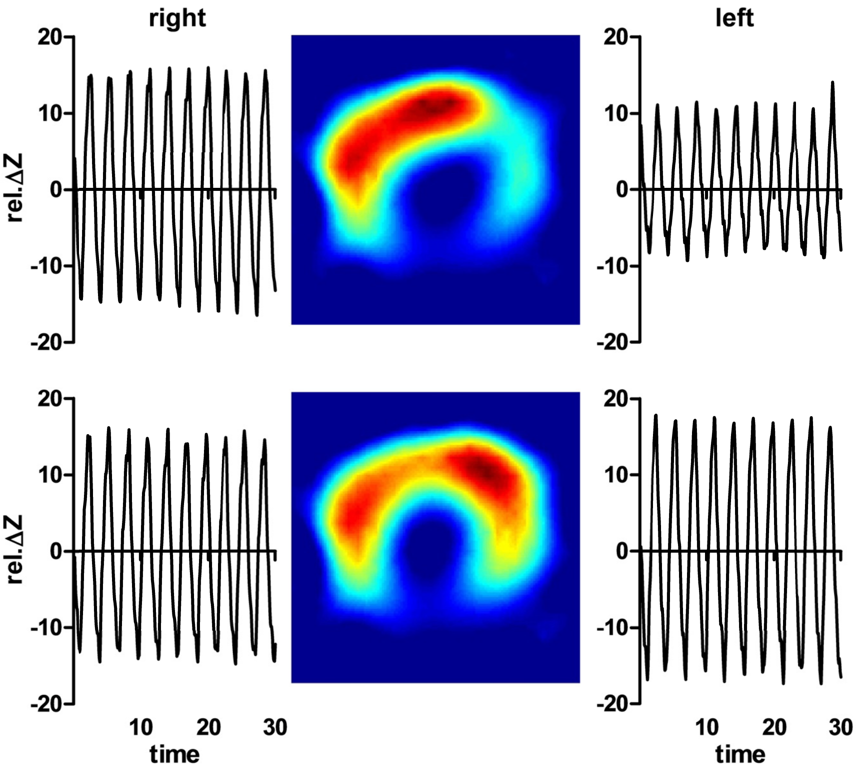

Figure E8.2. EIT examination of a 3-wk old intubated and mechanically ventilated term newborn with a body weight of 3340 g. EIT detected an asymmetric right-to-left ventilation distribution (top) which immediately disappeared after the correction of the tube position (bottom). The waveforms in the panels highlight the magnitude of ventilation in the right and left lungs. The orientation of the functional EIT ventilation images: anterior is at the top and the right side of the chest is on the left side of the image. (The raw data were recorded with the Goe-MF II EIT device (CareFusion, Höchberg, Germany).)

Common to all these studies was the observation that very simple real-time fEIT images, without complex post-hoc reconstruction, were useful in rapidly indicating the occurrence of an adverse event, and always before cardiorespiratory compromise. Using EIT within this context may be the simplest method of introducing EIT to clinical settings. Further studies are needed to determine whether EIT can identify adverse events earlier than current methods. The most meaningful outcome measures will need to be considered prior to conducting these studies, but should include radiation need, cost effectiveness as well as long-term outcomes such as mortality, morbidity and time to discharge.

The following Table E8.3 gives a summary of studies relevant for establishing the role of EIT in therapy guidance in neonatal/pediatric lung disease.

Clinical problem	Clinical inter-vention	Patient popu-lation	Type of lung disease	Mode of respiratory support	Type of EIT imaging	Physio-logical measure	Summary of results	Outcomes	References
Setting applied pressures	Open lung PEEP maneuver guided by EIT	12 piglets	Induced ARDS	Conventional ventilation	Raw data and fEIT images	EELV and regional V_T	EIT-guided recruitment strategy produced better gas exchange, lung mechanics and less lung injury than current ARDS-Net strategy	Suggests that EIT may be able to guide setting of the optimal applied pressure.	(12)
	Decremental PEEP trial, extubation	14 preterm infants	RDS	Conventional ventilation	fEIT ventilation images	U/L ventilation ratio	EIT-guided PEEP selection aimed at optimizing anteroposterior ventilation distribution and resulted in higher pressure values than the empirically chosen	EIT may be able to guide setting of the applied pressure after extubation during initiation of non-invasive ventilation support.	(76)
Identifi-cation of pneumo-thorax	Sequential introduction of gas into right pleural space	6 piglets	Induced ARDS	Conventional ventilation	Raw data and fEIT images	EELV, aeration maps and V_T	EIT was able to detect 10 mL of pleural gas, and significantly earlier than deoxygenation or bradycardia	EIT may identify pneumothoraces before clinical deterioration	(72)
	Case report	1 preterm infant	RDS	HFOV	fEIT image	V_T distribu-tion	fEIT image showed a decrease in tidal ventilation at the affected side	EIT was able to detect pneumothorax in preterm infants	(78)
Identifi-cation of atelectasis	Case report	1 preterm infant	RDS	nCPAP	fEIT ventilation images	V_T distribution	fEIT showed a decrease in tidal ventilation on the affected side	EIT was able to detect atelectasis in preterm infants	(79)

Clinical problem	Clinical inter-vention	Patient popu-lation	Type of lung disease	Mode of respiratory support	Type of EIT imaging	Physio-logical measure	Summary of results	Outcomes	References
Identifi-cation of recruitability and over-distension	Sustained inflation and stepwise recruitment	10 children	ARDS	Conventional ventilation	fEIT images of regional V_T and C_{rs}	Change in regional C_{rs} compared with best C_{rs} (80)	1. EIT identified responders and non-responders to recruitment maneuver. 2. Collapsed regions were better recruited by stepwise recruitment maneuver than sustained inflation. 3. Regional overdistension was more pronounced in non-responders but occurred in both groups.	EIT identified recruitable atelectasis and overdistension	(22)
Location of ETT position	Comparison of different clinical tools for detecting correct tracheal, single bronchus and oesophageal ETT location with EIT.	6 piglets	Induced ARDS	Conventional ventilation	Raw data and fEIT images	EELV, aeration maps and V_T.	Real time fEIT images were the only method that could identify oesophageal intubation, correctly located ETT and single bronchus intubation.	fEIT ventilation images may hold potential as a radiation-free method of determining the correct ETT position.	(40)
	Intentional brief single lung ventilation	18 intu-bated children during anaesthesia	Healthy	Conventional ventilation	fEIT images	Right and left lung V_T patterns	EIT identified: 1. Single lung ventilation due to ETT malposition. 2. Non-intended left main bronchus and oesophageal ETT placements in 2 children	fEIT may have potential to aid intubation during anesthesia	(41)

Clinical problem	Clinical inter-vention	Patient popu-lation	Type of lung disease	Mode of respiratory support	Type of EIT imaging	Physio-logical measure	Summary of results	Outcomes	References
Guiding resuscitation at birth	Delivery of a sustained lung inflation	35 preterm lambs	RDS	Neopuff™ and conventional ventilation	Raw data and fEIT	EELV and regional V_T	EIT-guided SI at birth resulted in better gas exchange, lung mechanics and less lung injury than a 30-s SI.	Suggest that EIT may be able to guide optimising respiratory support at birth.	(36)

Table E8.3. Summary of animal and human studies using of EIT to guide clinical care in pediatric and newborn lung disease.

ARDS: acute respiratory distress syndrome; C_{rs}: respiratory system compliance; EELV: end-expiratory lung volume; ETT: endotracheal tube; fEIT: functional EIT; HFOV: high-frequency oscillatory ventilation; nCPAP: nasal positive airway pressure; PEEP: positive end-expiratory pressure; RDS: respiratory distress syndrome; U/L: upper-to-lower; V_T: tidal volume

Practical limitations unique to infants and children

This section will focus on the limitations specific to the pediatric and infant population. In general these can be summarized as limitations related to the population itself, engineering and design and defining the clinical role. To date there are no suitable EIT systems available for clinical use in children and infants, this is despite the availability of a number of systems approved for adult use. The intrinsic factors that make EIT more attractive as a clinical tool in children and infants also create specific practical limitations that, to a certain extent, account for this discrepancy. The general limitations of EIT have been discussed in detail elsewhere, and most are as pertinent in children as adults, particularly the need for realtime image reconstruction and display.

The pediatric population has a greater variation in size, with any pediatric EIT system needing to adapt to patients from <500 g to >70 kg in weight. This offers unique problems relating to electrode design and also image reconstruction algorithms. In younger patients the small torso limits space for any monitoring, and the addition of EIT electrodes compete with other monitoring systems, such as transcutaneous gas monitoring. The close proximity with existing monitoring systems increases the risk of electrical interference and noise, especially in the already electrically crowded critical care environment (81). Newer systems, with better shielding should be able to negate these concerns. Although electrode interfaces exist for adults, it cannot be assumed that simply miniaturising adult designs will be appropriate for the pediatric population, who often have impaired skin integrity and need higher humidity environments. A single EIT patient interface, such as a flexible belt or band, containing an array of electrodes appears to be the most suitable solution in this population. Such an interface will need to be designed specifically for the shape, and movement, of the pediatric and infant chests, which varies considerably during the different developmental stages of childhood. At the same time, it must be sufficiently compliant to avoid constricting the chest. Image reconstruction will also need to consider these differences and use algorithms specifically designed for the patient population if clinicians are to be provided with accurate tomographic information, and thus maximize the potential for meaningful outcomes. To date, existing commercial EIT systems use a single algorithm designed for an adult chest shape and would not be suitable for children and infants. Movement artefact and electrode contact failure are likely to be higher in the non-compliant child and infant.

Which EIT parameters to display at the bedside, and in what format, have yet to be agreed upon. Fundamental questions such as whether to use absolute or relative images and which ones (for example ventilation, aeration and perfusion), whether EIT will simply be a diagnostic or a monitoring tool or specifically direct clinical care, and how to train clinicians to interpret EIT images need to be addressed before commercial systems, with broad and meaningful utility, will be possible.

Recommendations for future direction

The exact role of EIT in the pediatric and neonatal population, especially the critical care environment has yet to be systematically established and consensus statements are clearly needed. The goal of future research and device development should be to create practical and functional EIT systems in which the role of EIT in different clinical settings can be determined and then evaluated to ascertain whether benefits to outcome are possible. Through such an approach EIT is likely to become widely adopted.

Pediatric-specific electrode interfaces and image reconstruction algorithms are urgently needed. The growing market in pediatric and neonatal critical care, and particularly non-invasive respiratory support, justifies the commercial potential. These systems should be developed through collaboration between clinicians and medical equipment manufacturers so acceptable pediatric solutions are found. Electrode interfaces and display of information will need to be individualized to this diverse population and needs.

In the first instance, EIT is likely to be more easily adopted as a monitoring tool, particularly for early identification of simple adverse events and/or in environments where existing monitoring tools are impractical, particularly during non-invasive respiratory support. Such an approach will allow evaluation of the ability of EIT to alter existing high-risk practices (for example intubation) and investigations (chest radiography) without compromising safety and outcomes. From these experiences it is likely that the development of EIT systems that can be used to guide clinical practices, especially in the more meaningful but harder setting of applied pressures, can occur. The ultimate goal of such systems must be to demonstrate improvements in outcomes if EIT is to progress beyond a research tool in pediatric and neonatal practice.

Conclusions

Although EIT is a promising technique that provides the clinician valuable information on changes in lung aeration and perfusion, studies exploring its use to guide clinical practice are still lacking. Improvement in hardware, interface and software are urgently needed before EIT can take up this challenge. With these solutions it is likely that EIT will find a role in monitoring clinical care, especially during non-invasive ventilation.

Document preparation

The first draft of this online document was prepared by D. Tingay with collaboration of A. H. van Kaam, I. Frerichs, G. K. Wolf, A. Schibler, T. Riedel and P. C. Rimensberger. It was reviewed and approved by all other authors and collaborators.

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